Exhibit S

8242788

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

May 3, 2022

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *15/274,772*
FILING DATE: *September 23, 2016*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

Wanda Montgomery
Certifying Officer

PTO/AIA/14 (11-15)
Approved for use through 04/30/2016 OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN37
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stephen	Donald	WILTON	

Residence Information (Select One) US Residency ● Non US Residency Active US Military Service

City	Country of Residence	
Applecross		AU

Mailing Address of Inventor:

Address 1	18 Spey Road
Address 2	

City	Applecross	State/Province	
Postal Code	6153	Country	AU

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sue		FLETCHER	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Country of Residence	
Bayswater		AU

Mailing Address of Inventor:

Address 1	14 Roberts Street
Address 2	

City	Bayswater	State/Province	
Postal Code	6053	Country	AU

Inventor 3 Remove

Legal Name

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN37
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Graham		MCCLOREY	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Bayswater	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	3 Digwood Close		
Address 2			
City	Bayswater	**State/Province**	
Postal Code	6053	**Country** i	AU

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	123147		
Email Address	IPBoston.Docketing@nelsonmullins.com	Add Email	Remove Email

Application Information:

Title of the Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF		
Attorney Docket Number	AVN-008CN37	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	22	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country i

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Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	123147		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14/740097	2015-06-15
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/740097	Continuation of	13/741150	2013-01-14
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/741150	Continuation of	13/168857	2011-06-24
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/168857	Continuation of	12/837359	2010-07-15	8232384B	2012-07-31

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Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12/837359	Continuation of	11/570691	2008-01-15	7807816B	2010-10-05
Prior Application Status					Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
11570691	a 371 of international	PCTAU2005000943	2005-06-28		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.					Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
2004903474	AU	2004-06-28	
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN37
	Application Number	
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Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN37
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Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	The University of Western Australia		
Mailing Address Information For Applicant:			
Address 1	35 Stirling Highway		
Address 2			
City	Crawley	**State/Province**	
Country	AU	Postal Code	6009
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2016 OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN37
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Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Amy E. Mandragouras, Esq./			Date (YYYY-MM-DD)	2016-09-23
First Name	Amy	Last Name	Mandragouras	Registration Number	36,207

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AVN-008CN37
	Application Number	
Title of Invention	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 26, 2016
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN37 (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: 15/274,772 Confirmation No.: 1042

Filed: September 23, 2016 Art Unit: 1674

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF Examiner: Not Yet Assigned

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Dear Sir:

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

AMENDMENTS TO THE CLAIMS

1. **(Cancelled)**

2. **(New)** An antisense oligonucleotide of 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 17 consecutive bases of C AUU CAA CUG UUG CCU CCG GUU CUG AAG GUG (SEQ ID NO: 193), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

3. **(New)** A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 17 consecutive bases of C AUU CAA CUG UUG CCU CCG GUU CUG AAG GUG (SEQ ID NO: 193), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

REMARKS

Claim 1 was pending in the application. Claim 1 has been cancelled without disclaimer or prejudice to further prosecution in this or a related application. New claims 2 and 3 have been added. Applicants note that claims 2-3 are identical to claims 21-22, respectively, of U.S. Application No. 14/858,250 (expressly abandoned on January 22, 2016).

Support for new the claims can be found throughout the specification and claims as originally filed. Specifically, support for the term "morpholino antisense oligonucleotide" can be found at page 17, lines 1-5 (Table 1A) of the specification. Morpholino antisense oligonucleotides have been described in the literature. See, *e.g.,* Summerton, J. and Weller, D. (1997) Morpholino Antisense oligomers: design, preparation, and properties. *Antisense Nucl. Acid Drug Dev.*, 7, 187-195; Heasman, J. (2002) Morpholino Oligos: making sense of antisense? *Dev Biol* 243:209-214; and Gebski, B. *et al.* (2003) Morpholino antisense oligonucleotide induced dystrophin exon 23 skipping in *mdx* mouse muscle. *Hum. Mol. Gen.* 12(15): 1801-1811.

No new matter has been added. Accordingly, following entry of the foregoing amendment claims 2 and 3 will be pending in the application.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 202-4626. If a fee is due with this submission, please charge our Deposit Account No. 12-0080 under Order No. AVN-008CN37, from which the undersigned is authorized to draw.

Dated: September 26, 2016

Respectfully submitted,

Electronic signature: /Amy E. Mandragouras, Esq./
Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(800) 237-2000 (617) 742-4214 (Fax)
Attorney/Agent For Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/274,772	09/23/2016	Stephen Donald WILTON	AVN-008CN37	1042

123147 7590 09/18/2017

Nelson Mullins Riley & Scarborough LLP/Sarepta
One Post Office Square
Boston, MA 02109

EXAMINER
CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
1674	

NOTIFICATION DATE	DELIVERY MODE
09/18/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/274,772	Applicant(s) WILTON ET AL.	
	Examiner KIMBERLY CHONG	Art Unit 1674	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/30/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *2 and 3* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *2 and 3* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *06/30/2017*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 06/30/2017 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/30/2016 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 06/30/2017, claims 2 and 3 are pending and currently under examination.

Information Disclosure Statement

The submission of the Information Disclosure Statement on 06/30/2017, is in compliance with 37 CFR 1.97. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

New Rejections – necessitated by claim amendments

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2 and 3 are rejected under pre-AIA 35 U.S.C. 103(a) as being obvious over van Ommen (WO2004/083432 cited on IDS filed 09/26/2016), Koenig et al. (Nature 338, 509 - 511 06 April 1989 cited on IDS filed 09/26/2016) and Bennett et al. (WO 2011/72765 cited on IDS filed 09/26/2016).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The claims are drawn to an antisense oligonucleotide of 25 bases comprising a base sequence 100% complementary to consecutive bases of exon 53 of the human dystrophin pre-mRNA, wherein the antisense oligonucleotide base sequence comprises at least 20 consecutive bases of SEQ ID NO: 193, wherein uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain

and wherein the antisense induces exon 53 skipping. The claims are further drawn to a pharmaceutical composition comprising said antisense oligonucleotide.

van Ommen teach a genus of oligonucleotides 16-50 complementary to exon 53 and specifically teach an oligonucleotide h53AON1 that has 18 nucleotides identical to the claimed SEQ ID No. 193 (see Table 2) that causes skipping of exon 53. van Ommen et al. teach the oligonucleotides can be complementary to the exon in the pre-mRNA. Thus given the sequence of the DMD gene has been identified, as demonstrated by Koenig et al., an oligonucleotide sequence complementary to that portion of the mRNA is exactly determined by the simple base pairing rules of DNA and RNA (G being complementary to C, and A being complementary to T (or U)).

vanOmmen et al. the oligonucleotide can have modifications such as morpholino phosphorodiamidate, peptide nucleic acid and locked nucleic acids, for example, and further teach the oligonucleotide comprises modified internucleoside linkages (see claim 12 and page 23). The oligonucleotide taught by van Ommen et al. encompasses both DNA and RNA nucleic acids as well as nucleic acids that are a combination of DNA and RNA as stated on page 9: lines 9-10 “Any oligonucleotide fulfilling the requirements of the invention may be used to induce exon skipping in the DMD gene." van Ommen et al. teach different nucleic acids may be used to generate the oligonucleotide (see page 9 line 30 - page 10). Thus oligonucleotides in which uracil bases are thymine bases are encompassed in the meaning of ‘oligonucleotide’ taught by van Ommen et al.

van Ommen et al. do not specifically teach the oligonucleotide is chemically linked to a polyethylene glycol chain. Bennett et al. teach oligonucleotides for modifying

target gene expression and teach oligonucleotides that involve “chemically linking the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to…a polyethylene glycol chain (see page 17. line 33 to page 18, line 26).

It would have been obvious to one of ordinary skill in the art to make an antisense oligonucleotide of 25 bases comprising at least 20 bases of SEQ ID No. 193. Given van Ommen et al. teach a genus of oligonucleotides of up to 50 nucleotides in length, one of skill in the art would have been motivated to extend the sequence of h53AON1 to arrive at oligonucleotides of 25 nucleotides and having 20 nucleotides of SEQ ID No. 193. Because the mRNA sequence containing the exon 53 was known in the prior art, as shown by Keonig et al., the combination of these teachings provides motivation to prepare obvious variants of h53AON1 to try and optimize the activity of the oligonucleotide to prepare the most effective therapeutic for treating DMD.

It would have been routine and a common strategy to try and enhance the oligonucleotide by identifying variants of that oligonucleotide that have a higher level of activity and a common and efficient strategy for doing so is to synthesize and test longer oligonucleotides containing within them the sequence known to have the desired activity. Moreover it would have been obvious and routine to incorporate modifications such as a polyethylene glycol chain to enhance the activity, cellular distribution or cellular uptake of the oligonucleotide as taught by Bennett et al.

Applicant’s arguments that there was a high level of unpredictability in the field associated with selecting specific antisense oligonucleotides sequences to induce exon

skipping will be addressed given it is relevant to the new grounds for rejection. Applicant cites three references and sums the teachings up on page 12 of the response by stating the "references serve to illustrate the unpredictability associated with selecting specific antisense oligonucleotides that are effective for inducing exon skipping of dystrophin exons."

This argument is not persuasive because van Ommen et al. teach an oligonucleotide that is 18 nucleotides in length. There is no unpredictability in selecting an antisense oligonucleotide to induce exon 53 skipping given van Ommen et al. demonstrates such a compound. Koenig et al. describes the entire DMD cDNA sequence and therefore provides the sequences of exon 53 immediately surround the portion of exon 53 pre-mRNA demonstrated to be sensitive to exon 53 skipping. Thus, one of skill in the art would have a reasonable expectation of success that an oligonucleotide having longer that 18 nucleotides, for example a 25mer comprising at least 20 nucleotides of the claimed SEQ ID No. 193 would induce exon 53 skipping.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Claim Rejections - 35 USC § 102

The rejection of claims 2 and 3 under pre-AIA 35 U.S.C. 102(e) as being anticipated by van Ommen (US Application 20060147952 cited on IDS filed 09/26/2016) is withdrawn in response to claim amendments.

Claim Rejections - 35 USC § 103

The rejection of claims 2 and 3 under pre-AIA 35 U.S.C. 103(a) as being obvious over van Ommen (US Application 20060147952 cited on IDS filed 09/26/2016), van Ommen et al. (Patent 7,973,015 herein after “Patent ‘0156” cited on IDS filed 09/26/2016), Matteucci, M. (Perspectives in Drug Disc. and Design, 1996, vol. 4, pp 1-16 cited on IDS filed 09/26/2016) and evidence by Koenig et al. (Nature 338, 509 - 511 06 April 1989) is withdrawn in response to claim amendments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.

Claims 2 and 3are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

706.07(a) Final Rejection, When Proper on Second Action [R-07.2015]

Second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p). Where information is submitted in an information disclosure statement during the period set forth in 37 CFR 1.97(c) with a fee, the examiner may use the information submitted, e.g., a printed publication or evidence of public use, and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner. See MPEP § 609.04(b).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Kimberly Chong whose telephone number is 571-272-3111.** The examiner can normally be reached Monday thru Friday 9-5 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1674

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: November 16, 2017
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN37 (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: 15/274,772 Confirmation No.: 1042

Filed: September 23, 2016 Art Unit: 1674

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF Examiner: K. Chong

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. § 1.116

Dear Sir:

In response to the Final Office Action dated September 18, 2017 (Paper No. 20170911), finally rejecting claims 2 and 3, please amend the above-identified U.S. patent application as follows:

Listing of the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

LISTING OF THE CLAIMS

1. **(Cancelled)**

2. **(Previously Presented)** An antisense oligonucleotide of 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 20 consecutive bases of C AUU CAA CUG UUG CCU CCG GUU CUG AAG GUG (SEQ ID NO: 193), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide induces exon 53 skipping, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain; or a pharmaceutically acceptable salt thereof.

3. **(Previously Presented)** A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 20 consecutive bases of C AUU CAA CUG UUG CCU CCG GUU CUG AAG GUG (SEQ ID NO: 193), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide induces exon 53 skipping, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

REMARKS

Claims 2 and 3 are pending in the application. Applicants respectfully request reconsideration and withdrawal of the rejections as discussed below. Should the Examiner agree, she is urged to call the undersigned to address any outstanding double patenting rejections to expedite prosecution of this application.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being obvious over van Ommen *et al.* (WO 2004/083432), Koenig *et al.* (Nature 338, 509 - 511 06 April 1989) and Bennett *et al.* (WO 2011/72765). Applicants respectfully traverse this rejection based on the following remarks.

The Office has failed to establish a prima facie case of obviousness

To establish a *prima facie* case of obviousness, the Office must identify both a reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed, and why one of ordinary skill in the art would have considered the ***outcome predictable.*** *KSR Int'l Co. v. Teleflex, Inc.,* 550 U.S. 398 (2007). Given the deficiencies in the teachings of van Ommen *et al.*, Koenig *et al.* and Bennett *et al.*, there was no motivation to combine the teachings in the manner asserted by the Office. Moreover, given the significant level of unpredictability associated with selecting specific antisense oligonucleotide sequences to induce effective exon skipping, there was no predictability in a successful outcome even if one were to attempt to combine the teachings of the cited references.

The Office has failed to establish it would have been *prima facie* obvious to generate the claimed antisense oligonucleotide with ***all*** the elements provided in the claims. Specifically, the pending claims are drawn to an antisense oligonucleotide having the following elements: (i) 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA; (ii) 20 consecutive bases of SEQ ID NO: 193; (iii) uracil bases are thymine bases; (iv) the antisense oligonucleotide is a morpholino; (v) the antisense oligonucleotide induces exon 53 skipping; ***and*** (vi) the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

The Office relies on van Ommen *et al.* for teaching a genus of antisense oligonucleotides having 16-50 bases complementary to exon 53, and wherein the oligonucleotides can have modifications such as morpholino phosphorodiamidate, peptide nucleic acid and locked nucleic acids. *See* Office Action at page 4. The Office specifically relies on the teaching of an 18-base oligonucleotide (h53AON1), having 18 consecutive nucleotides of SEQ ID NO: 193. *Id.* Koenig *et al.* is relied upon for providing the full sequence of the entire DMD gene. *Id.* The Office asserts that given the sequence of the DMD gene, an oligonucleotide sequence complementary to that portion of the mRNA is exactly determined by the simple base pairing rules of DNA and RNA. *Id.*

The Office admits that van Ommen *et al.* do not specifically teach an oligonucleotide chemically linked to a polyethylene glycol chain, and therefore relies on Bennett *et al.* for teaching this limitation. *Id.* According to the Office, it would have been obvious to one of ordinary skill in the art to lengthen h53AON1 from 18-bases to make an antisense oligonucleotide of 25 bases comprising at least 20 bases of SEQ ID NO: 193 because van Ommen *et al.* teach a genus of oligonucleotides of up to 50 nucleotides in length, and therefore one of skill in the art would have been motivated to extend the sequence of h53AON1 to arrive at the claimed antisense oligonucleotide. *See* Office Action at page 5. The Office asserts the combination of these teachings provides motivation to prepare obvious variants of h53AON1 to try and optimize the activity of the oligonucleotide to prepare the most effective therapeutic for treating DMD. *Id.* Applicants respectfully disagree.

As an initial matter, Applicants wish to point out that there is absolutely nothing in van Ommen *et al.* about substituting uracil bases in RNA oligonucleotides with thymine bases. In fact the word "thymine" (or its structure) is not described anywhere in van Ommen *et al.* The Office suggests that van Ommen *et al.* implicitly disclose the use of thymine bases by arguing that "van Ommen et al. teach different nucleic acids may be used to generate the oligonucleotide…Thus oligonucleotides in which uracil bases are thymine bases are encompassed by the meaning of 'oligonucleotide' taught by van Ommen et al." Office Action at page 4. However, the term "DNA" appears nowhere in van Ommen *et al.* in the context of an antisense oligonucleotide having natural DNA bases. Rather, van Ommen *et al.* states that "[t]his view of the flow of genetic information has prompted the predominantly DNA-based approach for interfering with the protein content of a cell. This view is slowly changing and alternatives for interfering at the DNA level are being pursued," indicating that the invention

is an alternative to DNA-based approaches. *See* van Ommen *et al.* at ¶[0003]. Thus, the Examiner's assumption that van Ommen's statement that "[d]ifferent types of nucleic acid may be used to generate the oligonucleotide" (van Ommen *et al.* at ¶[0018]) necessarily is a disclosure of DNA as a nucleic acid that can be used to generate the oligonucleotide, and from this that the use of thymine bases is disclosed, is not supported by anything within the disclosure. Based on these teachings alone, one of skill in the art would not have been motivated to use DNA as presently claimed.

Further, none of the cited references teach or suggest combining the elements to result in the claimed antisense oligonucleotide. Specifically, there is no teaching or suggestion to generate an antisense oligonucleotide of 25 bases, wherein the antisense oligonucleotide comprises 20 consecutive bases of SEQ ID NO: 193, **and** wherein uracil bases are thymine bases, **and** wherein the antisense oligonucleotide is a morpholino, **and** wherein the resulting antisense oligonucleotide induces exon 53 skipping of the human dystrophin pre-mRNA. Therefore, one of ordinary skill in the art would have had no motivation to combine the teachings in the manner suggested by the Officer, and certainly not with a reasonable expectation of success.

Rather, the Office's proposed combination of the teachings of the cited references appears to suggest what may have been "obvious to try" would have been to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result." (*In re Kubin,* 561 F.3d 1351, 1359 (Fed. Cir. 2009)). As previously set forth in the Amendment in Response to Non-Final Office Action submitted June 30, 2017 (the "Response"), van Ommen *et al.* describe an empirical approach for the design of exon skipping antisense. *See* Response at page 6. This approach results in non-functional, out-of-frame transcripts, and there is no indication as to what parameters are critical for success. *See Id.* at page 7. Moreover, the results were unpredictable as van Ommen *et al.* report "[t]heir different lengths and G/C contents (%) ***did not correlate to their effectivity [sic] in exon skipping***". *Id.* at page 6 (*citing* van Ommen *et al.* Table 2, footnote a [0153]). Koenig *et al.* and Bennett *et al.* fail to provide any teaching or guidance that would make up for the deficiencies in van Ommen *et al.* Koenig *et al.* merely provides the sequence of the DMD gene, and Bennett *et al.* teach oligonucleotides for modifying gene expression.

Accordingly, the cited art provides no indication of what parameters were critical and no direction as to which of many choices is likely to be successful. Moreover, van Ommen *et*

al. demonstrate the results of testing various antisense oligonucleotides was not predictable. As such, the Office has failed to establish a *prima facie* case of obviousness based on the cited references and Applicants respectfully request reconsideration and withdrawal of this rejection.

High level of unpredictability in the field

With regard to Applicants previously submitted unpredictability arguments, the Office incorrectly asserts that "[t]here is **no unpredictability** in selecting an antisense oligonucleotide to induce exon 53 skipping given van Ommen *et al.* demonstrates [sic] such a compound. Thus, one of skill in the art would have a reasonable expectation of success that an oligonucleotide having longer than 18 nucleotides, for example a 25mer comprising at least 20 nucleotides of the claimed SEQ ID NO: 193 would induce exon 53 skipping." Office Action at page 6 (emphasis added). Applicants respectfully disagree.

The Office improperly and in contradiction to the Patent Trial and Appeal Board (PTAB) dismissed the objective evidence of unpredictability from those of skill in the art without providing any reason. As provided in the Response, this evidence shows that without sufficient guidance, modifying a starting antisense oligonucleotide is unpredictable. This same evidence was persuasive to the PTAB in Interference 106,007, as described in detail below.

During this proceeding, the critical issue considered by the PTAB was whether selecting an exon 53 skipping antisense oligonucleotide was unpredictable at the time US Application No. 11/233,495, was filed by Academisch Ziekenhis Leiden ("AZL"). Applicants note the '496 application claims priority to the van Ommen *et al.* PCT application presently cited by the Office. Substantial evidence regarding unpredictability at the time of the invention was submitted and considered by the PTAB. Applicants further note Exhibits 2010 and 2015 submitted in the Interference correspond to Aartsma-Rus and Wu *et al.*, previously submitted by Applicants as Appendices A and C, respectively, in the Response filed June 30, 2017.

Upon consideration of this evidence, the PTAB stated "[t]he evidence indicates that at the time AZL filed its application, the identification of AONs that will cause exon skipping was generally thought to be **unpredictable**. One of the significant factors causing that unpredictability is the effect of the number of nucleobases present in the AON." (Decision on

Motions at page 17 (emphasis added)). This unpredictability was maintained at the time of the instant invention.

Furthermore, similar to the Office's assertion, AZL argued that upon identification of h53AON1, "one skilled in the art would have investigated extended complementary sequences with the expectation that the longer sequences would bind and cause skipping." *Id.* The PTAB did not find this persuasive at least because AZL failed to provide any publications to support the basis for this expectation. *Id.* at page 18. Like AZL, the Office failed to provide publications to support this expectation. *See* Office Action at page 6. Accordingly, Applicants urge the Office to accept the PTAB's finding of unpredictability in the field of selecting an exon 53 skipping antisense oligonucleotide.

Moreover, the obviousness of changing the length of a base sequence of an antisense oligonucleotide shown to induce exon skipping was also considered by the PTAB. Like the Office Action, the Interference involved, *inter alia*, the 18-base h53AON1 and a 20-base AON sequence. *Id.* at pages 39-40. The PTAB found that "a degree of exon skipping capability would likely be maintained due to a change in a ***small number of complementary nucleobases*** of an AON known to cause skipping" and, therefore, concluded "[i]t would have been obvious, for example, to add the ***two*** complementary nucleobases dictated by the known sequence of exon 53 to either end of h53AON1 with a reasonable expectation that the resultant 20 base AON would cause exon skipping." *Id.* at pages 41-42 (emphasis added). In contrast to the issue considered by the PTAB's and its findings regarding adding ***2 bases*** to lengthen an 18-base sequence to a 20-base sequence, the presently claimed sequence is ***7 bases*** longer than the sequence provided in van Ommen *et al.* Accordingly, it would not have been obvious to extend h53AON1 by 7 bases at least because of the highly degree of unpredictability discussed above, and the Office failed to provide evidence to the contrary.

In summary, the Appendices previously submitted by Applicants along with the Decision of Motions from Interference 106,007, serve to illustrate the unpredictability associated with selecting specific antisense oligonucleotides that are effective for inducing skipping of dystrophin exons. Accordingly, the Office has failed to establish a *prima facie* case of obviousness with respect to the predictability of the outcome in combining teachings of van Ommen *et al.,* Koenig *et al.*, and Bennett *et al.* in the manner proposed to arrive at the claimed invention.

In view of the preceding remarks, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

Double Patenting

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636. Applicants respectfully request that this rejection be held in abeyance until allowable claims are indicated in the present application.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384. Applicants respectfully traverse this rejection.

The Office asserts "the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193." *Id.* However, Applicants note the instant claims are drawn to antisense oligonucleotide having at least 20 consecutive bases of SEQ ID NO: 193. Moreover, the '384 patent is directed to an antisense oligonucleotide *consisting* of SEQ ID NO: 195. '384 Patent at claim 1. Applicants point out that there is only a **9** base overlap between SEQ ID NOs: 193 of the '384 Patent and SEQ ID NO: 195 of the instant claims. As the present claims are directed to an antisense oligonucleotide having at least 20 consecutive bases of SEQ ID NO: 193, ***11 additional bases*** must be added to SEQ ID NO: 195 to arrive at the instant claims. Here, again, Applicants refer to the high degree of unpredictability discussed above and, accordingly, assert that the claims of the '384 patent and the instant claims are patentably distinct from each other. Applicants respectfully request reconsideration and withdrawal of the nonstatutory double-patenting rejection.

CONCLUSION

If a telephone conversation would expedite prosecution of the application and allowance of the claims, we invite the Examiner to call Applicants' representative at (617) 217-4626. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AVN-008CN37, from which the undersigned is authorized to draw.

Dated: November 16, 2017

Respectfully submitted,
Electronic signature: /Amy E. Mandragouras, Esq./
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